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REMARKS

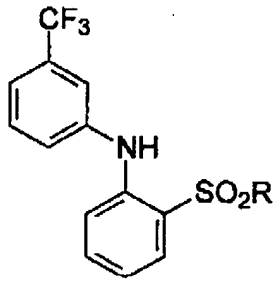
The Examiner has rejected Claims 1, 3, 4, 6-13 under 35 U.S.C. 103(a) as obvious in light of Gutman *et al* WO 03/097603 and Wouters *et al* Eur. J. Med. Chem. Vol. 35 pp 923-929.

Gutman et al

The Examiner states that Gutman *et al* page 13, steps f to h teaches the reaction of 4-*m*-tolyamino-3-pyridinesulfonamide, lithium (bi)carbonate and isopropylcarbamate in an aqueous solution. The Applicant has reviewed the page in question and did not find any reference to steps f to h. The Applicant notes that page 14 does include steps f to h. In contrast to the Applicants process, step f is used "to obtain an aqueous solution of the lithium salt of 4-*m*-tolylamino-3-pyridinesulfonamide". Furthermore, step g involves "reacting the aqueous solution of the lithium salt of [4-*m*-tolylamino-3-pyridinesulfonamide] with isopropyl carbamate". Claims 1, 3, 4, 6-13 of the Applicant's invention are all conducted in an organic solvent and not in an aqueous solution as per Gutman *et al*, and use isopropylisocyanate and not *iso*-propyl carbamate as per Gutman *et al*.

Wouters et al

The Examiner continues by stating that while Gutman *et al* does not teach the use of isopropylisocyanate, Wouters *et al* does. Specifically, the Examiner refers to lines 1-10 on page 928. Respectfully, the Applicant notes that in this procedure the authors reacted the sodium salt of 4-(3'-methylphenylamino)pyrid-3-yl sulfonamide in 1:1 water:acetone (not an organic solvent as per claims 1, 2, 4, 6-13) with isopropyl isothiocyanate (not isopropylisocyanate as per claims 1, 2, 4, 6-13) to form sulfonylthiourea **2** (not torsemide). The Wouters *et al* article does not include any experimental details documenting the synthesis of torsemide. The final sentence of page 927 Wouters states "The synthesis of compounds **1** [5] ... has been described previously. Reference 5 (Delarge J., Ann. Pharm. Fr. 31 (1973) 467-474) does not describe the preparation of torsemide. As can be seen in the English abstract on page 474, the article describes the "[t]he synthesis of chloro-4 pyridine sulfonic-3 acid and several functional derivatives ... having the general formula:"



Because torsemide does not possess a trifluoromethyl group, this reference cannot describe the synthesis of torsemide. Furthermore, as can be seen on page 469, none of the possible R groups corresponds to the urea functional group that torsemide possesses, therefore, no urea-forming reactions can be contained therein.

The Applicants believe that Wouters *et al* erred and instead meant to refer to their reference 6 (Delarge J., Ann. Pharm. Fr. 36 (1978) 369-380) which includes the synthesis of torsemide (see Table III, entry JDL 464 on page 375) using triethylamine, contrary to claims 1, 3, 4, 6-13 of the present application. If requested, an English translation of this article will be provided in a future correspondence. In the 1978 Delarge reference, a sulfonamide precursor to torsemide was reacted with isopropylisocyanate in neat triethylamine. The Applicants' claims 1, 3, 4, 6-13 specifically exclude triethylamine.

With respect to Claim 2, the Examiner points to page 12 step d as representative teaching. The Applicant notes that claim 2 has been previously cancelled. Respectfully, the Applicant fails to see the relevance of this example and requests further clarification.

Improper combination of the teachings of the prior art and lack of motivation to combine same

The Applicant also strongly disagrees with the Examiner suggestion that a combination of prior art teachings would achieve results identical to those of the Applicants' invention (see Figure 1 below for a hypothetical scenario where it clearly shows that torsemide will not be formed). Respectfully, the Applicant believes that the Examiner's suggestion that "isopropylisocyanate in aqueous solutions inherently forms isopropylcarbamate" is in error. The initial by-product of the reaction of an isocyanate with water is not a carbamate but the corresponding carbamic acid. The Applicant notes that N-isopropyl carbamic acid is not a suitable coupling partner with starting sulfonamide and will not generate the desired product but other decomposition products such as CO_2, *iso*-propyl amine and *iso*-propylurea.

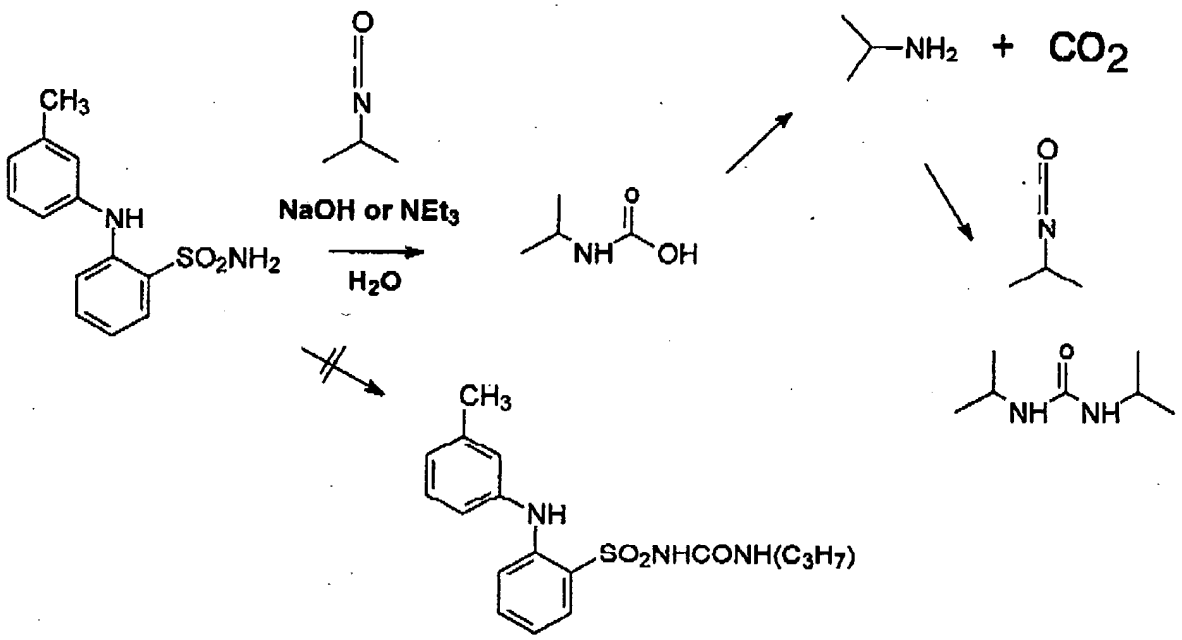


Figure 1 – Hypothetical combination of prior art teachings

Thus Gutman *et al* and Wouters *et al* are not properly combinable as their intended function, to generate torsemide, is destroyed. As such, a person having ordinary skill in the art would have no motivation or incentive to combine the teachings of these references.

The Examiner is respectfully directed to the following: "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification." In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

By this reasoning, Applicant respectfully submits that claims 1, 3, 4, 6-13 are not rendered obvious by the teachings of Gutman *et al* and Wouters *et al*. Applicant respectfully requests reconsideration by the Examiner of claims 1, 3, 4, 6-13.

In view of the above, the Applicant submits that claims 1, 3, 4, and 6-13 are unobvious and patentable over the Gutman *et* al WO 03/097603 in light of Wouters *et al* under 35 USC 103. Therefore, Applicant respectfully submits that the above-identified application is allowable.

If any questions arise, the Examiner is respectfully requested to contact Applicant's Agent, Marcelo K. Sarkis at (905) 771-6414 collect at the Examiner's convenience.

Respectfully submitted,
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Enclosure: Request for One Month Extension of Time